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Case Report

Chronic thromboembolic disease and necrotizing granulomatous vasculitis – A case report

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ABSTRACT

A 32 year old male presented to our services with severe, progressive breathlessness. Following a detailed clinical work-up he was found to have severe pulmonary arterial hypertension due to chronic thromboembolic disease. No risk factor for venous thromboembolism,was identified at this time. Vasculitic screen including anti-neutrophil cytoplasmic antibody (ANCA) was normal. He was referred for pulmonary artery endarterectomy which was performed successfully and with good initial improvement in his symptom complex. He represented with breathlessness four months later. He was diagnosed with necrotizing granulomatous vasculitis (known formerly as Wegner's Granulomatosis). While an association between necrotizing granulomatous vasculitis and venous thromboembolic disease is well described, to our knowledge this is the first case of a patient with chronic thromboembolic pulmonary hypertensive disease subsequently developing fulminant necrotizing granulomatous vasculitis.

To The Editors

While an association between necrotizing granulomatous vasculitis and venous thromboembolic disease is well described, we herein report case of a patient with chronic thromboembolic pulmonary hypertensive disease subsequently developing fulminant necrotizing granulomatous vasculitis.

A 32-year-old caucasian male farmer was referred to our centre, for investigation of progressive dyspnoea over 18 months. At review he had New York Heart Association (NYHA) functional class III-IV symptoms. He had a history of 2 previous pulmonary emboli without any identifiable risk factor for venous thrombolism (VTE). He was on lifelong warfarin, in accordance with international guidelines.[1] He was an ex-smoker, with a 12 pack year smoking history. His physical examination was notable for resting oxygen saturations of 96%, raised jugular venous pulse, loud second heart sound and pulsatile liver edge. His lung fields were clear to auscultation.

A transthoracic echo estimated his systolic pulmonary arterial pressure at 60 mmHg. High resolution CT thorax demonstrated mosaic attenuation pattern. A right heart catheterisation revealed a mean pulmonary arterial pressure of 65 mmHg with a normal pulmonary capillary wedge pressure. Notably, autoimmune screen, ANCA and thrombophilia screen were all negative.

He underwent pulmonary angiography at the national pulmonary hypertension unit which confirmed evidence of proximal thromboembolic disease. He was referred to the University of California Medical Centre, San Diego for a pulmonary thromboendarterectomy and in the interim he was maintained on bosentan and sildenafil. His endarterectomy was performed successfully and at initial review he had NYHA functional class II symptoms and was contemplating a return to work.

Unfortunately, 4 months later he presented with low grade fever, weight loss, non productive cough and malaise. A chest x-ray demonstrated multiple cavities (Fig. 1). A CT thorax confirmed the presence of new pulmonary cavities and nodules bilaterally (Fig. 2). His clinical work-up revealed c-ANCA positivity with an anti-proteinase 3 titre of 245 U/mL (normal <10U/mL). Bronchial lavage showed numerous haemosiderin-laden macrophages suggestive of pulmonary haemorrhage. He was diagnosed with necrotizing granulomatous vasculitis and commenced on steroids and oral cyclophosphamide. He responded well for an initial 8 month period and indeed returned to work, but 13 months post diagnosis, symptoms pertaining to pulmonary hypertension began to return and he was commenced on treprostenil.

Pulmonary hypertension is defined by a mean pulmonary arterial pressure $\geq$ 25 mmHg at rest, with a pulmonary capillary wedge pressure $\leq$ 15 mmHg assessed by right heart catheterization. The new classification of pulmonary hypertension divides the

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Fig. 1. Chest X-Ray demonstrating nodules and cavities bilaterally, most prominent in right lower zone.

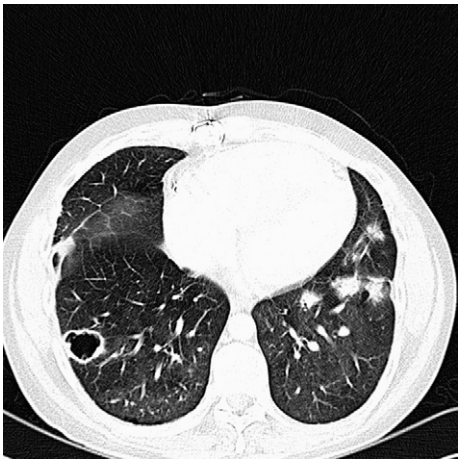

Fig. 2. CT image confirming the presence of multiple cavities and nodules seen on CXR.

condition into groups primarily by etiology and treatment response, with chronic thromboembolic pulmonary hypertension (CTEPH) placed in group 4. It occurs due to incomplete resolution of pulmonary thrombi, which undergo organisation in the pulmonary arteries with vascular remodelling and thromboendarterectomy, where proximal organised thrombus is accessible to surgical removal. There is some evidence to support the use of the endothelin receptor antagonist bosentan in CTEPH, in those considered inoperable or in an attempt to optimise pre-operative haemodynamics, targetted pulmonary arterial hypertension drug therapy may be considered.[2,3]

Necrotizing granulomatous vasculitis, is a small-medium vessel, necrotizing vasculitis of undetermined etiology (previously Wegner's Granulomatosis).[4] Clinical presentation varies from limited disease to a fulminant systemic disease. Diagnosis is often difficult and outcomes are variable.[5]

The risk of venous thromboembolism is increased in necrotizing granulomatous vasculitis. In the WeCLOT study 16% of patients demonstrated evidence of venous thromboembolism. This study followed patients with active necrotizing granulomatous vasculitis, looking for evidence of venous thromboembolism and found that the incidence of venous thromboembolism among patients with necrotizing granulomatous vasculitis was increased especially during periods of active disease.[6]

Our patient's presentation is unusual in that chronic thromboembolic disease developed years prior to any evidence of systemic vasculitis. At initial presentation we documented c-ANCA negativity. While c-ANCA negativity is reported in necrotizing granulomatous vasculitis and c-ANCA levels are known to fluctuate without therapeutic intervention, we believe this would be atypical, especially in the absence of systemic disease (other than perhaps VTE). Furthermore, our patient was c-ANCA positive at the time he represented with systemic manifestations of necrotizing granulomatous vasculitis suggesting that the disease represented a new clinical entity. However, it remains impossible to say definitively that he did not have subclinical, c-ANCA negative vasculitis from the start.

In summary, we present the unusual case of a man who developed severe pulmonary hypertension due to CTEPH who later developed necrotizing granulomatous vasculitis. While necrotizing granulomatous vasculitis has previously been associated with increased risk of subsequent development of chronic thromboembolic disease, this is, to our knowledge the first case of a patient developing the condition years following diagnosis, and indeed attempted definitive management of chronic thromboembolic disease.[6] It is unknown whether the chronic thromboembolic disease was an initial presenting feature of his necrotizing granulomatous vasculitis or whether the two processes have developed independently.

Conflict of interest

None.

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